Medical Staff Conference

Waldenström's Macroglobulinemia

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs Homer A. Boushey, Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and Associate Dean in the School of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

RICHARD K. ROOT, MD*: *Waldenström's macroglobulinemia is a particularly interesting B-cell lymphoplasmacytic neoplasm because so many of its clinical features are due to the monoclonal IgM protein found in the serum. Curt Ries, MD, Director of Faculty Practice in Hematology and Oncology of the Cancer Research Institute, will review the current concepts of diagnosis and treatment of this disorder.*

CURT A. RIES, MD†: Waldenström's macroglobulinemia is a well-differentiated B-cell lymphoplasmacytic neoplasm characterized by the presence of a monoclonal immunoglobulin (Ig) M protein in the serum and often associated with anemia, bleeding, and hyperviscosity.

Waldenström's macroglobulinemia accounts for about 5% of all malignant B-cell disorders associated with a monoclonal protein spike in the serum or urine, and about half of patients who have a monoclonal IgM spike in the serum have this disorder. The mean age of patients presenting with Waldenström's macroglobulinemia is 65 years, and about 60% of patients are men.

Weakness and fatigue are the most common presenting symptoms, followed by bleeding, particularly mucosal bleeding such as epistaxis and gastrointestinal bleeding (Table 1). Less common are weight loss, neurologic symptoms, visual symptoms, and Raynaud's phenomenon. The most common physical findings are hepatomegaly, splenomegaly, lymphadenopathy, and ocular changes. Neurologic abnormalities, purpura, and congestive heart failure are less common.[1-6]

Anemia is the most common laboratory abnormality at the time of diagnosis. Anemia is usually mild or moderate but may be severe, requiring erythrocyte transfusions. The leukocyte and platelet counts are usually normal. Other laboratory abnormalities include an elevated serum viscosity in the majority of patients. Cryoglobulinemia occurs in about a third of patients. Bence Jones proteinuria is often found if the urine is concentrated.

There are several causes for the bleeding diathesis in Waldenström's macroglobulinemia.[7] The most important factor leading to mucocutaneous bleeding is distention of the cutaneous and mucosal capillary beds due to the increased plasma volume caused by the elevated IgM level. Platelet function is also commonly impaired because of the presence of the IgM protein on the platelet surface. The abnormal protein may also inhibit fibrin polymerization and in rare cases appears to specifically inhibit factor VIII or other clotting factors. There are also reports of clotting factors being consumed in cryoprecipitates or other precipitated protein complexes.

The anemia in Waldenström's macroglobulinemia may also have several causes. Anemia is in part due to the increased plasma volume caused by the elevated IgM level in the plasma.[8] This is a dilutional anemia and is associated with a minimal decrease in the red cell volume. Many patients with Waldenström's macroglobulinemia also have a hypoproliferative anemia due to bone marrow infiltration with abnormal lymphocytes and plasma cells.

Some patients have a hemolytic anemia due to the presence of cold agglutinins. In these patients the monoclonal IgM also has cold agglutinin activity. Finally, because of the bleeding tendency in patients with this disorder, anemia due to blood loss or iron deficiency is relatively common.

In general, there is a direct correlation between the degree of elevation of IgM in the serum, the degree of increase in serum viscosity, and the degree of plasma volume expansion and dilutional anemia.[8] Symptoms are unusual in patients with Waldenström's macroglobulinemia when the IgM level is below 3.0 grams per dl or the relative serum viscosity is less than 3.0. Increases in the IgM level above 3.0 grams per dl are usually associated with significant increases in serum viscosity and progressive symptoms. Slight increases in the relative serum viscosity, in the range of 3.0 to 5.0, are usually associated with weakness, fatigue, and exertional dyspnea, but not with severe neurologic or visual symptoms. Serum viscosity levels of greater than 5.0 usually are associated with more serious symptoms, and when the serum viscosity is greater than 10, a full-blown hyperviscosity syndrome usually occurs.

The clinical features of the hyperviscosity syndrome include bleeding, particularly epistaxis, gastrointestinal bleeding, cutaneous bleeding, and retinal hemorrhage.[9] The eye findings can include the presence of dilated or sausage-shaped veins, hemorrhage, retinal vein thrombosis, and papilledema.

Neurologic symptoms include fatigue, weakness, headache, vertigo, paresis, confusion, seizures, and coma. Finally, the hyperviscosity syndrome is associated with hypervolemia, which manifests itself clinically as congestive heart failure, although cardiac function may be completely normal.

The diagnosis of Waldenström's macroglobulinemia is usually based on the finding of a monoclonal IgM spike in the serum, which usually is greater than 1.5 grams per dl at the

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time of diagnosis. Anemia is present in most patients. Although lymphadenopathy and hepatosplenomegaly are common, these findings are variable, and their absence does not exclude the diagnosis (Table 2).

Before a diagnosis of Waldenström's macroglobulinemia can be made, other B-cell neoplasms associated with a monoclonal IgM protein must be excluded. These include chronic lymphocytic leukemia, lymphocytic lymphomas, multiple myeloma, mixed cryoglobulinemia, and cold agglutinin disease. If the IgM spike is less than 1.5 grams per dl, it may initially be difficult to differentiate Waldenström's disorder from monoclonal gammopathy of an undetermined significance.

The differential diagnosis between Waldenström's macroglobulinemia, well-differentiated lymphocytic lymphoma, and chronic lymphocytic leukemia is usually apparent; at times, however, there may be some overlap that will lead to confusion (Table 3).

In chronic lymphocytic leukemia, there must be lymphocytosis (15,000 per μl) in the peripheral blood. In Waldenström's macroglobulinemia and lymphocytic lymphomas, there may be abnormal cells present in the peripheral blood, but there is rarely lymphocytosis to this degree.

The degree of lymphadenopathy and hepatosplenomegaly is usually more subtle in patients with Waldenström's disorder than in those with chronic lymphocytic leukemia or lymphocytic lymphoma. The essential feature that usually distinguishes patients with this disorder from those with well-differentiated lymphocytic lymphoma is the degree of elevation of the IgM protein. Although a fraction of patients with lymphocytic lymphomas do have a small IgM spike in their serum, the amount of IgM is usually small compared with that in patients with Waldenström's macroglobulinemia.

The appearance of the abnormal B cells in the bone marrow or on histologic sections of bone marrow or lymph node biopsy specimens may be very similar in patients with Waldenström's disorder, those with chronic lymphocytic leukemia, and those with well-differentiated lymphocytic lymphoma. Immunologic characterization of the B cells in these three disorders may also be inconclusive. The presence of morphologically typical plasmacytoid lymphocytes, however, favors the diagnosis of Waldenström's macroglobulinemia.

Differentiating between multiple myeloma and Waldenström's macroglobulinemia is usually easy based on the type of immunoglobulin present in the monoclonal spike. The vast majority of patients with multiple myeloma have either IgG or IgA present in their serum or free light chains present in their urine. Patients with Waldenström's, on the other hand, have only IgM paraproteins. The clinical features of these two disorders are compared in Table 4. In rare cases, so-called IgM multiple myeloma has been described. These patients have IgM paraproteins, but also have lytic bone lesions and other clinical features that are usually only found in multiple myeloma.

In addition to the common presentations of Waldenström's macroglobulinemia previously noted, patients occasionally present with renal disease, pulmonary disease, or neurologic problems (Table 1). Various renal abnormalities have been described.[10] Most patients have Bence Jones proteinuria, although excretion is usually less than 1 gram per 24 hours. About a third of patients have significant nonselective proteinuria. Between 20% and 30% of patients have some degree of renal insufficiency, although, unlike the case in multiple myeloma, severe renal failure is rare. Pathologic changes in the kidney include IgM deposits in capillary loops, focal amyloidosis, interstitial infiltration with lymphocytes and plasma cells, and, rarely, immunologically mediated glomerulonephritis.[11]

TABLE 1.—*Clinical Presentations of Waldenström's Macroglobulinemia*

Common Presentations
Immunoglobulin M spike seen on protein electrophoresis
Weakness, fatigue
Anemia
Bleeding
Hepatosplenomegaly, lymphadenopathy
Uncommon Presentations
Hyperviscosity syndrome
Raynaud's phenomenon, other cryopathic symptoms
Renal disease
Pulmonary disease
Peripheral neuropathy

TABLE 2.—*Diagnostic Features of Waldenström's Macroglobulinemia*

Presence of an immunoglobulin M spike on serum protein electrophoresis and immunoelectrophoresis—usually greater than 1.5 grams per dl
Normocytic anemia usually present
Hepatosplenomegaly, lymphadenopathy (variable)
Bone marrow usually shows increased plasmacytoid lymphocytes, lymphocytes, or plasma cells
Exclude chronic lymphocytic leukemia, lymphoma, multiple myeloma, mixed cryoglobulinemia, cold agglutinin disease, monoclonal gammopathy of undetermined significance

TABLE 3.—*Differential Diagnosis of Malignant B-Cell Disorders Associated With Monoclonal Immunoglobulin M Spikes*

Diagnostic Feature	*Waldenström's Macroglobulinemia*	*Chronic Lymphocytic Leukemia*	*Lymphocytic Lymphoma*
Immunoglobulin M spike	+++	+	+
Hyperviscosity	++	−	−
Peripheral blood lymphocytosis	−	+++	+/−
Hepatosplenomegaly, lymphadenopathy	+	++	+++
Anemia	++	+/−	+/−
Bleeding	++	+/−	−
Infection	−	+	+/−
Bone marrow failure	+	++	+/−

+ = infrequent or not prominent, ++ = more prominent, +++ = very prominent, − = absent

Patients with pulmonary involvement with Waldenström's macroglobulinemia present with dyspnea, nonproductive cough, and, less commonly, chest pain.[12] Chest x-ray findings include diffuse interstitial or focal infiltrates, pulmonary nodules, hilar masses, and pleural effusions. These findings are similar to those seen in patients with advanced chronic lymphocytic leukemia and lymphocytic lymphoma.

A mixed sensorimotor neuropathy often develops in patients with Waldenström's macroglobulinemia similar to that occurring in patients with multiple myeloma.[13] The neuropathy is slowly progressive and becomes disabling in a small proportion of patients. In some of these patients, the IgM paraprotein has been shown to have antimyelin activity in vitro.

Treatment of Waldenström's macroglobulinemia depends primarily on the degree of elevation of the IgM paraprotein, which in turn determines the severity of symptoms. Patients with low levels of IgM and serum viscosity of less than 3.0 usually do not require treatment. As the IgM level increases, dilutional anemia occurs, as well as symptoms related to increased blood viscosity. Patients with serum viscosities between 3.0 and 5.0 may or may not require treatment, depending on symptoms. Patients with serum viscosities of 5.0 or greater almost always require treatment. Often patients with Waldenström's disorder attribute the most common symptoms of the disease—weakness, fatigue, and shortness of breath—to advancing age, because of the gradual onset and slow progression of these symptoms.

The therapy for Waldenström's macroglobulinemia includes erythrocyte transfusions, plasmapheresis, and chemotherapy (Table 5). Erythrocyte transfusions are most useful in patients with hypoproliferative anemias due to bone marrow infiltration. Dilutional anemia due to the increased IgM levels and corresponding increase in plasma volume is best treated by plasmapheresis. These patients have a near-normal red cell volume.

TABLE 4.—*Clinical Features of Multiple Myeloma and Waldenström's Macroglobulinemia*

	Multiple Myeloma	*Waldenström's Macroglobulinemia*
Monoclonal protein	IgG,IgA,LC	IgM
Hyperviscosity	+/−	++
Lytic bone lesions	+++	−
Anemia	+++	++
Bleeding	+	++
Infection	+++	−
Hypercalcemia	++	−
Nephropathy	++	+
Neuropathy	++	++
Bone marrow failure	++	+
Hepatosplenomegaly, lymphadenopathy	−	+

IgA=immunoglobulin A, IgG=immunoglobulin G, IgM=immunoglobulin M, LC=light chain, +=infrequent or not prominent, ++=more prominent, +++=very prominent, −=absent

TABLE 5.—*Treatment of Waldenström's Macroglobulinemia*

No treatment required—about a third of patients
Erythrocyte transfusions
Plasmapheresis
Chemotherapy
- Alkylating agents—chlorambucil, cyclophosphamide, melphalan—with or without prednisone
- Combination chemotherapy—cyclophosphamide, vincristine sulfate, prednisone (CVP); cyclophosphamide, melphalan, carmustine, vincristine, prednisone (M-2 protocol)

Plasmapheresis can be done either by the traditional bag method or by using a blood cell separator. In the bag method, a unit of blood is removed from the patient and centrifuged, the plasma is removed, and the cells are returned to the patient. This procedure can be done two to four times over a period of several hours, with removal of 600 to 1,200 ml of plasma. The main advantage of bag plasmapheresis is that it is relatively simple to do, has little risk, and does not require specialized equipment. The main limitation of bag plasmapheresis is that a relatively limited amount of plasma can be removed, so that it is not suitable for rapidly reducing the serum viscosity in patients with serious or life-threatening hyperviscosity symptoms.

Plasmapheresis using cell separators has the advantage that large amounts of plasma can be removed in relatively short periods of time. Typically, 2,000 to 4,000 ml of plasma is removed in a single pheresis session lasting two to three hours. When such large volumes of plasma are removed, volume must be replaced with plasma substitutes such as albumin or plasma protein fractions.

This type of plasmapheresis is the treatment of choice for patients with serious or life-threatening hyperviscosity. After initially controlling hyperviscosity by plasmapheresis as noted above, maintenance plasmapheresis can be done at periodic intervals using either the bag method or a cell separator to try to maintain the serum viscosity in an acceptable range.

Chemotherapy can be used to control excessive IgM production in Waldenström's macroglobulinemia and is useful in treating patients who are symptomatic and who cannot be controlled by plasmapheresis, or who require such frequent plasmapheresis that this form of therapy becomes unacceptable to them or their physicians. Chemotherapy should be initiated cautiously, as some patients with Waldenström's macroglobulinemia seem to be sensitive to chemotherapy, with granulocytopenia or thrombocytopenia readily developing. This is particularly the case for patients who have substantial bone marrow infiltration.

Various chemotherapy regimens have been used for treating patients with Waldenström's macroglobulinemia. Generally an alkylating agent, usually chlorambucil, is given initially either in a continuous low dose or in a pulsed fashion, with or without prednisone. Cyclophosphamide and melphalan have also been used. Combination chemotherapy using cyclophosphamide, vincristine sulfate, and prednisone or more intensive combinations such as the M-2 protocol (Table 5) have also been used.[14]

In general, the lower dose, less toxic chemotherapy should be tried first and the treatment escalated only if it is justified by a patient's symptoms and clinical course. High-dose intensive chemotherapy that produces severe bone marrow hypoplasia is rarely warranted in patients with Waldenström's macroglobulinemia.

The median survival is about 50 months. This survival time depends heavily on the exclusion of higher grade B-cell malignant disorders associated with IgM monoclonal proteins. Particularly, advanced chronic lymphocytic leukemia, higher grade lymphomas, and IgM myeloma must be excluded, as they have a poorer prognosis. Likewise, it is important to exclude patients with IgM monoclonal gammopathy of an undetermined significance, as these patients have a better prognosis.

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Acute Aortic Defects

MANY PATIENTS who are now being seen in the emergency room with chest pain are being considered for thrombolytic therapy. Obviously, the administration of thrombolytic therapy, whether it is streptokinase or tissue plasminogen activator in a patient with aortic dissection masquerading as a myocardial infarction, has very important implications in terms of patient welfare, as well as medicolegal implications. I suspect we may well see more and more of these reports, since the message that we are receiving from people very active in this area is that if we are going to make a significant impact and salvage myocardium during the acute phase of myocardial infarction, the thrombolytic therapy has to be given very early, and generally, it is given without catheterization and confirmation of coronary occlusion.

Now, the relationship of the site of pain to the origin of dissection is an important point. Most proximal dissections will be associated with anterior chest pain. In contrast, patients with distal dissections, type III dissections versus type I or type II, typically will present with back pain—posterior pain. Again, though, there is some variability, and the key is to ask the patient to describe the quality of pain: it is usually excruciating; it is usually tearing; it is usually maximal in intensity at outset.

Other less common presenting symptoms include syncope. In patients with dissection who present with syncope, the mechanism is almost always acute pericardial tamponade, although, rarely, significant hemorrhage into either the pleural space or the mediastinum will cause syncope. But syncope means pericardial tamponade. The presence of a pericardial effusion in a patient with a high probability of dissection is associated with an extremely high mortality. Roughly 75% of patients with pericardial effusions and dissections are dead within 24 hours if surgical therapy is not carried out.

Transient ischemic attack (TIA) and stroke, because of branch vessel occlusion; pulse loss, with or without ischemic pain; and also, congestive heart failure—these patients almost always have aortic regurgitation.

Finally, painless dissection can occur. It is very rare, and the majority of these patients at the time of presentation exhibit disturbed consciousness. If they were able to give a history, whether or not they would complain of chest pain is not clear in reviewing the history.

—ROBERT S. GIBSON, MD

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